

## Short communication

# Tolerability, safety, and efficacy of adjunctive brivaracetam for focal seizures in older patients: A pooled analysis from three phase III studies



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## ABSTRACT

**Introduction:** This analysis was conducted to assess the tolerability, safety, and efficacy of brivaracetam (BRV) for adjunctive treatment of focal (partial-onset) seizures in patients aged  $\geq 65$  years.

**Methods:** Safety/tolerability and efficacy data for patients aged  $\geq 65$  years were pooled from three randomized, double-blind, placebo-controlled, fixed-dose Phase III studies (NCT00490035, NCT00464269, and NCT01261325). Data were pooled by treatment group: placebo or the proposed therapeutic dose range of 50–200 mg/day: BRV 50, 100, 200 mg/day.

**Results:** Thirty-two patients aged  $\geq 65$  years were randomized to placebo or BRV 50–200 mg/day. Of these, 30 patients (93.8%) completed their respective study. In the safety population ( $n = 32$ ), 87.5% placebo- vs 73.3% BRV-treated patients reported treatment-emergent adverse events (TEAEs) during the treatment period; most commonly, headache (25.0% vs 12.5%), paresthesia (0% vs 12.5%), and somnolence (50.0% vs 12.5%) for placebo- vs BRV-treated patients, respectively. During the treatment period, drug-related TEAEs were reported by 62.5% of placebo- vs 53.3% of BRV-treated patients, and serious TEAEs (SAEs) were reported by 0% of placebo- and 4.2% of BRV-treated patients; there were no drug-related SAEs and no deaths. Three SAEs (placebo 1/8; BRV 2/24) and two deaths (placebo 1/8; BRV 1/24) occurred in the post-treatment period. In the efficacy population ( $n = 31$ ), median percent reduction from baseline in focal seizure frequency/28 days was 14.0% for placebo vs 25.5%, 49.6%, and 74.9% for BRV 50, 100, and 200 mg/day, respectively. The  $\geq 50\%$  responder rate was 14.3% for placebo vs 25.0%, 50.0%, and 66.7% for BRV 50, 100, and 200 mg/day, respectively.

**Conclusions:** Safety/tolerability and efficacy findings in this small subgroup of older patients treated with adjunctive BRV are consistent with those observed in the much larger overall pooled population. BRV may be a suitable adjunctive treatment for older patients with uncontrolled focal seizures. Further larger studies in this population are warranted.

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## 1. Introduction

Epilepsy is common in older adults; causes of new-onset epilepsy at older ages include cerebrovascular disease, dementia,

Alzheimer's, brain tumor, primary neurodegenerative disorders, and traumatic head injury (Brodie et al., 2009; Pugh et al., 2009). The incidence of treated epilepsy has been estimated at 80.8 per 100,000 in the general population, rising to 85.9 per 100,000 in those aged 65–69 years, and 135.4 per 100,000 in people  $\geq 85$  years (Wallace et al., 1998). In addition to older patients with new-onset epilepsy, the population of older adults with epilepsy also includes those who have been treated for many decades.

The mortality rates for people diagnosed with epilepsy are 3.1, 1.7, and 2.0 times greater than the general population for those aged 60–69, 70–79, and  $\geq 80$  years (Lhatoo et al., 2001). Age-associated effects on antiepileptic drug (AED) pharmacokinetics (PK) and pharmacodynamics mean that AED selection and dosages may need

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adjustment in this population (Turnheim, 2003). Older patients are often receiving concomitant drugs for multiple comorbidities. Therefore, enzyme induction by some AEDs poses a particular challenge for optimal polypharmacy in older patients (Brodie et al., 2013; Perucca, 2006).

There are relatively few randomized controlled trials of AEDs in older populations. The evidence base currently supports the use of lamotrigine or levetiracetam (LEV) as a first-line AED in older patients with epilepsy (Brodie et al., 1999; Rowan et al., 2005; Saetre et al., 2007; Werhahn et al., 2015).

Brivaracetam (BRV), a selective, high-affinity synaptic vesicle protein 2A ligand, has been approved by the USA, Canada, and Europe as adjunctive therapy for focal seizures in adults ( $\geq 16$  years) with epilepsy. A study in 16 older healthy volunteers found that BRV was well tolerated, with adverse events comparable to a younger population (Sargentini-Maier et al., 2009). The objective of the current analysis was to assess the tolerability, safety, and efficacy of BRV for adjunctive treatment of focal seizures in older patients. This article reports a post-hoc analysis of pooled data from three pivotal studies which enrolled patients aged  $\geq 65$  years (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014).

## 2. Methods

### 2.1. Study designs

The methodology and study designs have been published for the three randomized, double-blind, placebo-controlled, fixed-dose Phase III studies used in this analysis (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014). After an 8-week prospective baseline period, patients received placebo or BRV (5–200 mg/day), initiated without up-titration for a 12-week treatment period. The studies were conducted in accordance with accepted guidelines and all patients provided written informed consent before study enrolment.

### 2.2. Participants

The three studies enrolled patients with focal seizures, with or without secondary generalization, uncontrolled on 1–2 AEDs. Studies NCT00490035 and NCT00464269 included adults aged 16–70 years  $\geq 45$  kg. Study NCT01261325 included adults aged 16–80 years  $\geq 40$  kg. Patients were required to have  $\geq 2$  focal seizures/month during the 3 months before baseline, and  $\geq 8$  focal seizures during the 8-week baseline period (with  $\geq 2$  focal seizures during each 4-week period in study NCT01261325). In two studies, concomitant LEV was limited to 20% of the population; in study NCT01261325 concomitant LEV was not allowed.

### 2.3. Endpoints and statistical analysis

Tolerability and safety endpoints were treatment-emergent adverse events (TEAEs), laboratory assessments, vital signs, and electrocardiograms (ECGs) during the treatment period. Efficacy endpoints included median percent reduction in focal seizure frequency from baseline/28 days,  $\geq 50\%$  responder rate ( $\geq 50\%$  reduction in focal seizure frequency from baseline), and seizure freedom rate (all seizure types) during the treatment period.

Data from the three studies were pooled; further details are presented elsewhere (Ben-Menachem et al., 2016). Data were pooled by treatment group for the approved dose range of 50–200 mg/day: BRV 50, 100, 200 mg/day or placebo. This post-hoc analysis included patients aged  $\geq 65$  years.

The safety population comprised patients taking  $\geq 1$  dose of study drug. The efficacy population comprised patients from the primary efficacy analyses: the intent-to-treat (ITT) population in

studies NCT00490035 and NCT01261325, and the modified ITT population in study NCT00464269, who were not receiving LEV at study entry.

## 3. Results

### 3.1. Patient disposition

Overall, 1558 patients were randomized, of whom 38 were aged  $\geq 65$  years. Of these, 32 patients were randomized to placebo ( $n=8$ ) or BRV 50–200 mg/day ( $n=24$ ) and are included in the safety population of this analysis. In total, 30/32 patients (93.8%) completed their respective studies; 2/32 (6.3%) discontinued due to adverse events.

### 3.2. Patient demographics and baseline characteristics

At baseline, patients  $\geq 65$  years had a mean (standard deviation [SD]) age of 72.1 (4.2) years vs 69.3 (3.6) years, and 57.1% and 54.2% were male, in the placebo and BRV groups, respectively. Patients had a long duration of epilepsy (mean [SD] duration: 24.8 [14.7] vs 34.1 [20.6] years), and median focal seizure frequency/28 days at baseline was 9.6 vs 7.5, for the placebo and BRV groups, respectively. Most patients had discontinued  $\geq 2$  prior AEDs; more than half had previously discontinued LEV. The most common concomitant AEDs were oxcarbazepine, carbamazepine, lamotrigine, and lacosamide (Table 1).

### 3.3. Safety and tolerability

In patients aged  $\geq 65$  years ( $n=32$ ), mean (SD) drug exposure was 81.1 (12.0) days for placebo and 82.6 (18.0) days for BRV.

Altogether, 7/8 (87.5%) placebo vs 16/24 (66.7%) BRV patients reported TEAEs during the treatment period (Table 2). Of these, 5/8 (62.5%) placebo vs 13/24 (54.2%) BRV patients reported drug-related TEAEs. Few patients discontinued study drug due to TEAEs: 1/8 (12.5%) patients on placebo and 1/24 (4.2%) patients on 100 mg/day BRV. The most commonly reported TEAEs were headache (placebo 2/8; 25.0% vs BRV 3/24; 12.5%), paresthesia (0/8; 0% vs 3/24; 12.5%), and somnolence (4/8; 50.0% vs 3/24; 12.5%) (Table 2).

During the treatment period, serious TEAEs (SAEs) were reported by no placebo patients and one BRV-treated patient (a 76-year-old woman receiving BRV 100 mg/day fell after a seizure resulting in hematoma, kidney injury, and a broken rib; BRV was permanently discontinued). No drug-related SAEs or deaths were reported during the treatment period.

After core study completion, SAEs were reported by one placebo- and two BRV-treated patients. A 70-year-old woman receiving BRV during long-term follow-up fractured her pelvis in an accidental fall (considered unrelated to study drug), which resolved. A 68-year-old man previously receiving placebo died from septicemia and a 70-year-old man previously receiving BRV 100 mg/day had a septic infection (after 8 days the patient went into septic shock, BRV was withdrawn, and after 3 weeks the patient died). Both deaths were thought unlikely related to study drug.

Patient numbers were small; however, there were no trends of clinical concern in the laboratory assessments.

### 3.4. Efficacy

In patients aged  $\geq 65$  years ( $n=31$ ), median percent reduction from baseline in focal seizure frequency/28 days was 14.0% (placebo) vs 25.5%, 49.6%, and 74.9% (BRV 50, 100, and 200 mg/day, respectively) (Fig. 1A). Similarly, the  $\geq 50\%$  responder rate was 1/7 (14.3%) for placebo vs 1/4 (25.0%), 7/14 (50.0%), and 4/6 (66.7%)

**Table 1**Patient demographics and baseline characteristics in patients aged  $\geq 65$  years ( $n = 31$ ).

	Placebo ( $n = 7$ )	BRV 50 mg/day ( $n = 4$ )	BRV 100 mg/day ( $n = 14$ )	BRV 200 mg/day ( $n = 6$ )	BRV overall ( $n = 24$ )
Mean (SD) age, years	72.1 (4.1)	68.8 (1.9)	70.0 (4.1)	67.8 (3.2)	69.3 (3.6)
Male gender, $n$ (%)	4 (57.1)	1 (25.0)	9 (64.3)	3 (50.0)	13 (54.2)
Mean BMI (SD), $\text{kg}/\text{m}^2$	24.8 (5.3)	27.4 (2.8)	27.9 (4.0)	28.0 (4.2)	27.8 (3.7)
Race, $n$ (%)					
White	5 (71.4)	4 (100.0)	14 (100.0)	6 (100.0)	24 (100.0)
Asian	1 (14.3)	0	0	0	0
Other <sup>a</sup>	1 (14.3)	0	0	0	0
Etiology, $n$ (%)					
Idiopathic	2 (28.6)	0	2 (14.3)	1 (16.7)	3 (12.5)
Symptomatic	2 (28.6)	3 (75.0)	5 (35.7)	3 (50.0)	11 (45.8)
Cryptogenic	3 (42.9)	1 (25.0)	7 (50.0)	2 (33.3)	10 (41.7)
Unknown	0 <sup>b</sup>	0	0	0	0
Mean (SD) [range] duration of epilepsy, years	24.8 (14.7) [3–48]	45.9 (13.0) [28–58]	27.2 (17.6) [3–53]	42.2 (26.8) [2–69]	34.1 (20.6) [2–69]
Median (minimum–maximum) focal seizure frequency/28 days at baseline	9.6 (6, 71)	15.4 (4, 37)	6.8 (4, 17)	7.5 (4, 12)	7.5 (4, 37)
Number of prior AEDs, $n$ (%)					
0–1	1 (14.3)	0	3 (21.4)	1 (16.7)	4 (16.7)
2–4	3 (42.9)	4 (100.0)	5 (35.7)	2 (33.3)	11 (45.8)
$\geq 5$	3 (42.9)	0	6 (42.9)	3 (50.0)	9 (37.5)
Prior LEV treatment, $n$ (%)	4 (57.1)	3 (75.0)	7 (50.0)	4 (66.7)	14 (58.3)
Concomitant AEDs <sup>b</sup> , $n$ (%)					
Oxcarbazepine	0	1 (25.0)	6 (42.9)	1 (16.7)	8 (33.3)
Carbamazepine	1 (14.3)	3 (75.0)	2 (14.3)	1 (16.7)	6 (25.0)
Lamotrigine	1 (14.3)	0	2 (14.3)	1 (16.7)	3 (12.5)
Lacosamide	1 (14.3)	0	1 (7.1)	2 (33.3)	3 (12.5)

Note: The efficacy population comprised all patients from the primary efficacy analyses in studies N01252, N01253, and N01358, excluding patients receiving concomitant LEV in studies N01252 and N01253. AED, antiepileptic drug; BMI, body mass index; BRV, brivaracetam; LEV, levetiracetam; SD, standard deviation.

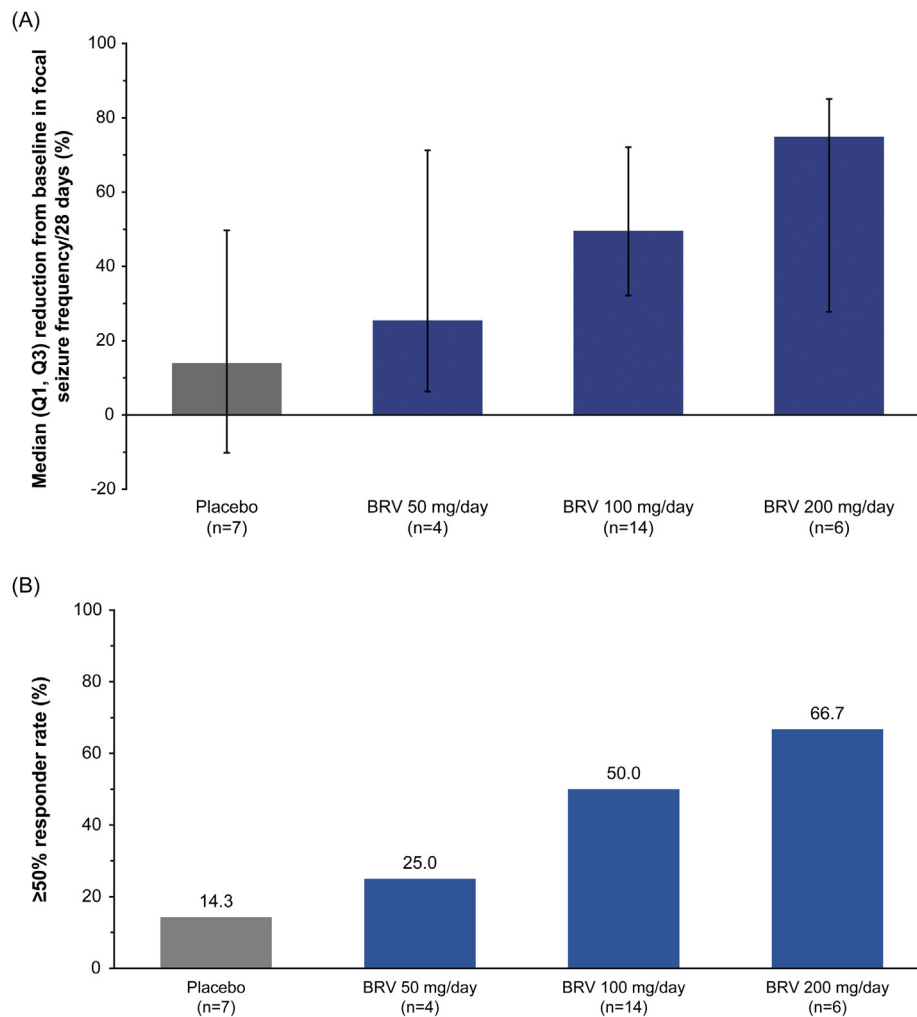
<sup>a</sup> Other race includes black, other, and missing.

<sup>b</sup>  $\geq 10\%$  in BRV overall group.

**Table 2**Summary of TEAEs and most commonly reported TEAEs during the treatment period ( $n = 32$ ).

Patients, $n$ (%)	Placebo ( $n = 8$ )	BRV 50 mg/day ( $n = 4$ )	BRV 100 mg/day ( $n = 14$ )	BRV 200 mg/day ( $n = 6$ )	BRV overall ( $n = 24$ )
$\geq 1$ TEAE	7 (87.5)	3 (75.0)	9 (64.3)	4 (66.7)	16 (66.7)
TEAEs leading to discontinuation of study drug	0	0	1 (7.1)	0	1 (4.2)
Drug-related TEAEs	5 (62.5)	3 (75.0)	6 (42.9)	4 (66.7)	13 (54.2)
SAEs	0	0	1 (7.1)	0	1 (4.2)
Drug-related SAEs	0	0	0	0	0
Deaths	0	0	0	0	0
TEAEs reported by $\geq 5\%$ patients in the overall BRV group, $n$ (%)					
Headache	2 (25.0)	1 (25.0)	1 (7.1)	1 (16.7)	3 (12.5)
Paresthesia	0	1 (25.0)	2 (14.3)	0	3 (12.5)
Somnolence	4 (50.0)	0	2 (14.3)	1 (16.7)	3 (12.5)
Cataract	0	1 (25.0)	1 (7.1)	0	2 (8.3)
Constipation	0	0	2 (14.3)	0	2 (8.3)
Convulsion	0	0	2 (14.3)	0	2 (8.3)
Cystitis	0	0	2 (14.3)	0	2 (8.3)
Hyponatremia	0	0	1 (7.1)	1 (16.7)	2 (8.3)

Note: The safety population comprised all patients randomized to placebo or BRV dosages of  $\geq 50$  mg/day, who received  $\geq 1$  dose of BRV, regardless of any concomitant treatment with LEV. BRV, brivaracetam; LEV, levetiracetam; SAE, serious treatment-emergent adverse event; TEAE, treatment-emergent adverse event.



**Fig. 1.** (A) Median percent reduction from baseline in focal seizure frequency/28 days and (B) ≥50% responder rate for focal seizure frequency, in the efficacy population ( $n = 31$ ).

BRV, brivaracetam; Q, quartile.

for BRV 50, 100, and 200 mg/day, respectively (Fig. 1B). Efficacy appeared to increase with increased BRV dosage, although the patient numbers were small. The number of patients continuously free of seizures (all seizure types) were 0/7 (placebo) vs 3/24 BRV (1/4, 1/14, and 1/6 patients for BRV 50, 100, and 200 mg/day, respectively).

#### 4. Discussion and conclusions

In this small subgroup of older patients treated with adjunctive BRV, a comprehensive evaluation of TEAEs and laboratory assessments did not reveal any issues of clinical concern. Seizure control rates were higher with BRV than placebo and compared favorably with those observed in the much larger overall pooled population (Ben-Menachem et al., 2016). Indeed, seizure reduction rates were higher than for the overall population. It should be noted that the population analyzed here had a long epilepsy duration and the majority had received  $\geq 2$  prior AEDs; they were therefore not typical of patients with new-onset epilepsy at older ages.

BRV has several characteristics which make it a potentially favorable choice for older patients, although appropriate caution should be taken for this population; a lower dose may be necessary for patients with decreased hepatic, renal, or cardiac function. BRV has a low potential to induce or inhibit the cytochrome (CYP) sys-

tem (Chanteux et al., 2015), except for CYP2C19 which is involved in secondary metabolism of BRV (Sargentini-Maier et al., 2008). It acts as a moderate inhibitor of epoxide hydrolase (Stockis et al., 2015). In the pivotal trials, BRV showed a favorable safety and tolerability profile and titration was not required for tolerability reasons (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014).

Limitations of this analysis include its post-hoc nature and the small number of patients aged  $\geq 65$  years. A higher age cut-off or further age stratifications might be useful in future studies, as might studies in patients with late-onset epilepsy.

Based on these results, BRV may be a suitable adjunctive treatment for older patients with uncontrolled focal seizures. The tolerability and safety profile was similar to, and efficacy rates were higher than, the overall pooled population. However, owing to the small number of patients in this analysis, further studies in older patients are warranted.

#### Disclosures

Martin J. Brodie consults on advisory boards for Bial, Eisai, GlaxoSmithKline, GW Pharmaceuticals, Lundbeck, Takeda, and UCB Pharma, and has made presentations at symposia for Eisai, GlaxoSmithKline, Sanofi Aventis, and UCB Pharma. John Whitesides is an employee of UCB Pharma, and reports personal fees from UCB

Pharma during the conduct of the study and outside the submitted work. Jimmy Schiemann was an employee of UCB Pharma at the time that the original studies and this analysis were conducted; he is currently an employee of Teva Pharmaceuticals. Joseph D'Souza is an employee of UCB Pharma and reports personal fees from UCB Pharma outside the submitted work. Martin E. Johnson is an employee of UCB Pharma and receives salary, stock options, and benefits from UCB Pharma.

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## References

- Ben-Menachem, E., Mameniškienė, R., Quarato, P.P., Klein, P., Gamage, J., Schiemann, J., Johnson, M.E., Whitesides, J., McDonough, B., Eckhardt, K., 2016. Efficacy and safety of brivaracetam for partial-onset seizures in three pooled clinical studies. *Neurology* 87 (3), 314–323.
- Biton, V., Berkovic, S.F., Abou-Khalil, B., Sperling, M.R., Johnson, M.E., Lu, S., 2014. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. *Epilepsia* 55, 57–66.
- Brodie, M.J., Overstall, P.W., Giorgi, L., 1999. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res.* 37, 81–87.
- Brodie, M.J., Elder, A.T., Kwan, P., 2009. Epilepsy in later life. *Lancet Neurol.* 8, 1019–1030.
- Brodie, M.J., Mintzer, S., Pack, A.M., Gidal, B.E., Vecht, C.J., Schmidt, D., 2013. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia* 54, 11–27.
- Chanteux, H., Kervyn, S., Gerin, B., Rosa, M., Latour, N., Stockis, A., Nicolas, J.-M., 2015. *In vitro* pharmacokinetic profile of brivaracetam reveals low risk of drug–drug interaction and unrestricted brain permeability. *Epilepsy Curr.*, 333 (Abstract No: 332.310).
- Klein, P., Schiemann, J., Sperling, M.R., Whitesides, J., Liang, W., Stalvey, T., Brandt, C., Kwan, P., 2015. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. *Epilepsia* 56, 1890–1898.
- Lhatoo, S.D., Johnson, A.L., Goodridge, D.M., MacDonald, B.K., Sander, J.W., Shorvon, S.D., 2001. Mortality in epilepsy in the first 11–14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann. Neurol.* 49, 336–344.
- Perucca, E., 2006. Clinically relevant drug interactions with antiepileptic drugs. *Br. J. Clin. Pharmacol.* 61, 246–255.
- Pugh, M.J., Knoefel, J.E., Mortensen, E.M., Amuan, M.E., Berlowitz, D.R., Van Cott, A.C., 2009. New-onset epilepsy risk factors in older veterans. *J. Am. Geriatr. Soc.* 57, 237–242.
- Rowan, A.J., Ramsay, R.E., Collins, J.F., Pryor, F., Boardman, K.D., Uthman, B.M., Spitz, M., Frederick, T., Towne, A., Carter, G.S., Marks, W., Felicetta, J., Tomyanovich, M.L., 2005. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. *Neurology* 64, 1868–1873.
- Ryvlin, P., Werhahn, K.J., Blaszczyk, B., Johnson, M.E., Lu, S., 2014. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. *Epilepsia* 55, 47–56.
- Saetre, E., Perucca, E., Isojarvi, J., Gjerstad, L., on behalf of the LAM 40089 Study Group, 2007. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. *Epilepsia* 48, 1292–1302.
- Sargentini-Maier, M.-L., Espie, P., Coquette, A., Stockis, A., 2008. Pharmacokinetics and metabolism of 14C-brivaracetam, a novel SV2A ligand, in healthy subjects. *Drug Metab. Dispos.* 36, 36–45.
- Sargentini-Maier, M.-L., Homery, M.C., Stockis, A., on behalf of the Brivaracetam N01118 Study Group, 2009. Pharmacokinetics, safety and tolerability of brivaracetam in healthy elderly subjects. *Epilepsia* 50 (4), 113.
- Stockis, A., Chanteux, H., Rosa, M., Rolan, P., 2015. Brivaracetam and carbamazepine interaction in healthy subjects and in vitro. *Epilepsy Res.* 113, 19–27.
- Turnheim, K., 2003. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp. Gerontol.* 38, 843–853.
- Wallace, H., Shorvon, S., Tallis, R., 1998. Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet* 352, 1970–1973.
- Werhahn, K.J., Trinka, E., Dobesberger, J., Unterberger, I., Baum, P., Deckert-Schmitz, M., Kniess, T., Schmitz, B., Bernedo, V., Ruckes, C., Ehrlich, A., Kramer, G., 2015. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. *Epilepsia* 56, 450–459.